546. *Reactions of Fluorine-substituted Acylarylnitrosamines.*

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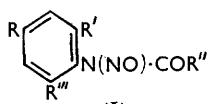
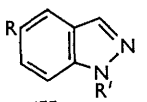
When acylarylnitrosamines containing fluorine *para* or *ortho* to the nitrosamine group are made to decompose in dry benzene, partial replacement of the fluorine by an acyloxy-group (derived from the acyl part of the molecule) occurs. This phenomenon is discussed in relation to the currently accepted mechanism [1,2,3] of such decompositions.

Elsewhere [4] we have reported that *N*-(4-fluoro-*o*-tolyl)-*N*-nitrosobenzamide (I; R = F, R′ = Me, R″ = Ph, R‴ = H) cyclises in dry benzene to give the expected 5-fluoroindazole (II; R = F, R′ = H) and an approximately equal amount of a water-insoluble, fluorine-free solid. This substance formed a nitroso-compound and a silver salt and when hydrolysed with acid yielded 5-hydroxyindazole (II; R = OH, R′ = H) and benzoic acid. Benzoylation of the unknown substance and of authentic 5-hydroxyindazole produced the same dibenzoyl derivative (II; R = BzO, R′ = Bz), as confirmed by the identity of their ultraviolet spectra. The above reactions as well as analytical data show the substance to be 5-benzoyloxyindazole (II; R = BzO, R′ = H). Purification and analysis of the nitroso-compound (I; R = F, R′ = Me, R″ = Ph, R‴ = H), as well as the absence of fluorine ions in the mother-liquor from which it separated, rule out the possibility of fluorine replacement during the nitrosation. Moreover, the purity of the nitroso-compound was also demonstrated by a quantitative denitrosation with sulphuric acid.

No replacement occurred when fluorine occupied a position *meta* to the acylnitrosamine group,[4] nor could we detect replacement of chlorine in the preparation of 5-chloroindazole (II; R = Cl, R′ = H) from the chloro-compound (I; R = Cl, R′ = Me, R″ = Ph, R‴ = H). The case in which fluorine is *ortho* to the *N*-nitroso-group could not be studied as we failed in the preparation of *N*-(6-fluoro-*o*-tolyl)-*N*-nitrosobenzamide (I; R = H, R′ = Me, R″ = Ph, R‴ = F).



(I)



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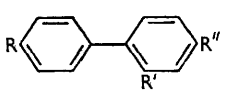

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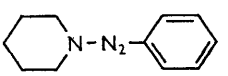


(IV)

It was obviously of interest to ascertain whether fluorine would be displaced in acylarylnitrosamines without an *ortho*-methyl group.

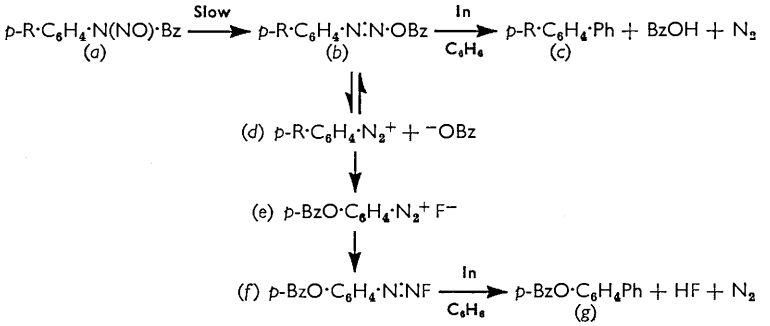
From a benzene solution of *N*-(4-fluorophenyl)-*N*-nitrosobenzamide (I; R = F, R′ = R‴ = H, R″ = Ph) that was stored for two days at room temperature, the expected 4-fluorobiphenyl (III; R = F, R′ = R″ = H) and 4-benzoyloxybiphenyl (III; R = BzO, R′ = R″ = H) were isolated in approximately equal amount. An analogous result was obtained with *N*-(4-fluorophenyl)-*N*-nitrosoacetamide (I; R = F, R′ = R‴ = H, R″ = Me), which yielded a mixture of the fluoro-compound (III; R = F, R′ = R″ = H) and 4-acetoxybiphenyl (III; R = AcO, R′ = R″ = H) (separated as 4-hydroxybiphenyl). From the acetamide (I; R = R‴ = H, R′ = F, R″ = Me) and the benzamide (I; R = R‴ = H, R′ = F, R″ = Ph) 2-fluoro- and 2-hydroxy-biphenyl were produced when, after decomposition was complete, the reaction mixture was treated with boiling sodium hydroxide solution. No fluorine replacement occurred, however, with *N*-*m*-fluorophenyl-*N*-nitrosobenzamide in which fluorine occupies a position *meta* to the *N*-nitroso-group.

The presence of acyloxyphenyl radicals was established by using nitrobenzene as solvent in one of the decompositions: from *N*-*p*-fluorophenyl-*N*-nitrosobenzamide (I; R = F,

[1] Hey, Stuart-Webb, and Williams, *J.*, 1952, 4657.
[2] Huisgen and Horeld, *Annalen*, 1949, **562**, 137.
[3] De Tar and De Los, *J. Amer. Chem. Soc.*, 1951, **73**, 1446.
[4] Barben and Suschitzky, *J.*, 1960, 672.

R′ = R‴ = H, R″ = Ph) a mixture of 4-benzoyloxy-2′-nitro- (III; R = BzO, R′ = NO_2, R″ = H) and 4-benzoyloxy-4′-nitro-biphenyl (III; R = BzO, R′ = H, R″ = NO_2) was produced, a result which is typical of " homolytic aromatic substitution."

A mechanism of the decomposition of acylarylnitrosamines in solution was first advanced by Hey and his collaborators,[5,6] who also demonstrated that the subsequent arylation was homolytic in nature,[7] an interpretation that was corroborated by Waters.[8] More recently, as a result of Huisgen and Horeld's work,[2] which was confirmed and extended by Hey *et al.*,[1] the rate-determining step of the decomposition, previously assumed to involve homolysis of a diazo-ester [*e.g.*, (*b*)] into free radicals, was shown to be the isomerisation of the acylarylnitrosamine (*a*) to the diazo-ester (*b*). We believe that the ready replacement of fluorine when in *ortho*- or *para*-position to the diazo-ester group constitutes direct chemical evidence for the occurrence of ionic dissociation of the covalent diazo-ester [*e.g.* (*b*; R = F)] to give a diazonium cation and an acid anion (*d*; R = F) undoubtedly present as an ion-pair. The reaction steps leading from here to fluorine replacement and consequently to formation of a mixture of biphenyls are clear and can be set out as annexed:

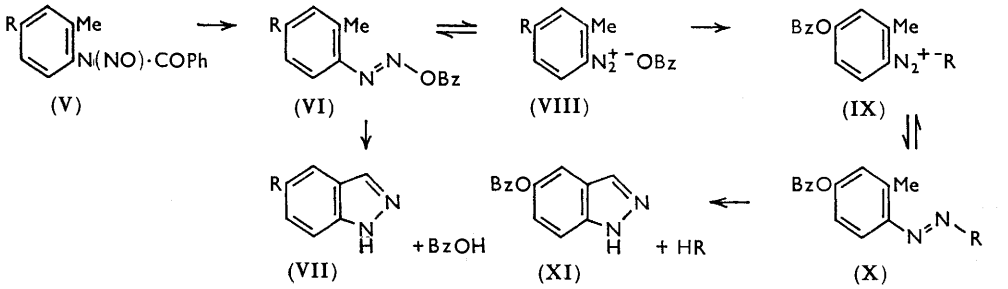


Stages (*a*), (*b*), and (*c*) (in each case R = F) represent the recently modified scheme [1,2] of the decomposition and phenylation of acylarylnitrosamines, accounting for the formation of the expected 4-fluorobiphenyl (stage *c*; R = F). The postulated heterolysis of (*b*) leads to the ion-pair (*d*). Replacement of fluorine by the nucleophilic acid anion is now strongly facilitated because of the outstanding effect of an *ortho*- or *para*-situated diazonium group in accelerating such substitutions,[9] to which fluorine is particularly susceptible. As a result of this nucleophilic substitution a new ion-pair (*e*) may be formed in which the fluoride ion is functioning as the anionic partner, and which may combine to form a new covalent diazo-ester (*f*). Its subsequent decomposition is analogous to that of the diazo-compound (*b*), yielding 4-benzoyloxybiphenyl (*g*) and hydrogen fluoride which is found in the reaction mixture.

The ease and extent of fluorine replacement which we observed in the preparation of 5-fluoroindazole are also best accounted for by a nucleophilic substitution. Such a process, *e.g.*, for the nitroso-compound (V; R = F) can be well accommodated within the scheme of mechanism which Huisgen and Nakaten [10] have recently postulated for the Jacobson indazole synthesis as follows: the nitroso-compound (V; R = F) undergoes a rate-determining isomerisation to the *trans*-diazo-ester (VI; R = F) which cyclises to indazole (VII; R = F) by a four-centre type of reaction. It is recognised that a non-polar solvent is most conducive to the reaction. We suggest that a reversible heterolysis of the diazo-ester (VI; R = F) into a diazonium cation and an acid anion (VIII; R = F) has to be

[5] Grieve and Hey, *J.*, 1934, 1797.
[6] Butterworth and Hey, *J.*, 1938, 116.
[7] Hey, Nechvatal, and Robinson, *J.*, 1951, 2892.
[8] Waters, *J.*, 1937, 113.
[9] Bunnett and Zahler, *Chem. Rev.*, 1951, **49**, 273.
[10] Huisgen and Nakaten, *Annalen*, 1954, **586**, 84.

added to the above reaction scheme. Thus fluorine becomes extremely vulnerable to attack by the negative partner of the ion-pair (VIII), the benzoate anion. As a result of the " nuisance effect " of a diazonium group,[9] a mixture of two indazoles (VII and XI; R = F) is obtained by cyclisation of the nitroso-compound (V; R = F). The formation



of the latter indazole from the covalent diazo-ester (X; R = F) produces hydrogen fluoride and compound (XI; R = F).

Ability of a covalent diazo-ester to undergo heterolysis has been postulated before, *e.g.*, the existence of an equilibrium between the covalent diazo-form and the corresponding ionic diazonium compound in acetic acid was inferred by Huisgen and Horeld [2] on kinetic grounds for the coupling reaction of acylarylnitrosamines with β-naphthol. The possibility of such an equilibrium was, however, excluded for benzene solutions. Similarly, De Tar and De Los [3] suggest that benzenediazonium cations are formed by heterolysis of benzenediazoacetate in methanol. The assumption that a diazo-ester may be a source of diazonium ions was also made by Hey *et al.*[1] in order to explain formation of the triazen-like compound (IV) in the reaction of *N*-nitrosoisobutyranilide with piperidine. Moreover, a polar mechanism involving the diazonium cation was put forward by Hodgson [11] as an alternative to the free-radical hypothesis of arylation. It is, however, unlikely that the diazonium cation which derives considerable stability through resonance will decompose in preference to the less stable diazo-ester. The possibility that free radicals are originated by decomposition of a diazonium cation rather than by fission of a covalent diazo-compound can also be ruled out, since radical formation *via* the cation would give rise to an ionised nitrogen molecule (N_2^+), a process which is energetically most unfavourable.

The formation of phenolic esters in our experiments could supposedly arise from replacement of the fluorine by acyloxy-radicals. Such an interpretation, however, neither covers the observation that solely fluorine in certain positions is affected, nor is it consistent with our knowledge of the usual behaviour of such radicals, although certain heteroaromatic acyloxy-radicals appear to be capable of replacing " aromatic halogen." [12]

By using nucleophilically activated fluorine as a " label," the occurrence of heterolysis in a non-polar solvent has been demonstrated in reactions of at least certain fluorine-substituted acylarylnitrosamines. The question naturally arises whether ionic tendencies in benzene solution are confined to those diazo-esters possessing fluorine substituents. So far there appears to be no recorded observation of any other atom or group undergoing anionic replacement in arylation with acylarylnitrosamines. A consideration of the basic electronic properties of " aromatic fluorine " makes it unlikely that induction of unsymmetrical cleavage could be a prerogative of this halogen alone. Although the resultant electronic tendencies of " aromatic halogens " differ, they are usually similar in magnitude.[13,14] In fact, we hope shortly to demonstrate experimentally that acylarylnitrosamines are prone to intermediate ion-pair formation in benzene, regardless of the nature of their substituents.

[11] Hodgson, *J.*, 1948, 348.
[12] Ford and Mackay, *J.*, 1957, 4620; 1958, 1290, 1294.
[13] Groves and Sugden, *J.*, 1937, 1992.
[14] Dippy *et al.*, *J.*, 1934, 161, 1888; 1935, 343; 1936, 644.

Experimental

Ultraviolet measurements (for MeOH solutions) were made with a Unicam S.P. 500 instrument.

5-Benzoyloxyindazole.—The water-insoluble solid (1·6 g.) obtained as a by-product from the preparation of 5-fluoroindazole [4] was chromatographed in benzene on alumina (Spence type "H," 100—200 mesh) and eluted with benzene containing ethanol (1% by vol.). Recrystallisation of the solid contained in the first runnings (1 l.) from benzene–light petroleum (b. p. 100—120°) gave *5-benzoyloxyindazole* as needles, m. p. 164·5—165·5° (0·8 g.) (Found: C, 70·4; H, 4·7. $C_{14}H_{10}N_2O_2$ requires C, 70·6; H, 4·2%), $\lambda_{max.}$ 233, 283 mμ (log ε 4·25, 3·65). Later eluants yielded a small quantity of a solid, m. p. 266—268°, which was not further investigated.

Denitrosation of N-(*4-Fluoro-o-tolyl*)-N-*nitrosobenzamide.*—(*a*) The nitroso-compound (0·1 g.) was dissolved in concentrated sulphuric acid (0·5 ml.). When dissolution was complete the mixture was poured into cold water, a white solid (0·08 g., 91%) being precipitated and nitrous fumes evolved. A mixed m. p. with *N*-(4-fluoro-*o*-tolyl)benzamide was undepressed.

(*b*) Denitrosation in ethanol with zinc and acetic acid was not quantitative.

5-Hydroxyindazole.—Hydrolysis of 5-benzoyloxyindazole (0·15 g.) with hydrochloric acid (2·5 ml.; *d* 1·18) under reflux for 1 hr. gave a precipitate of benzoic acid. Neutralisation of the filtered mother-liquor with ammonia and extraction with chloroform yielded 5-hydroxyindazole, m. p. and mixed m. p. with an authentic specimen [15] 185—186°. Benzoylation of the hydroxy-compound in pyridine with benzoyl chloride produced *1-benzoyl-5-benzoyloxyindazole* as needles (from ethanol), m. p. 184—185° (Found: C, 74·1; H, 4·1. $C_{21}H_{14}N_2O_3$ requires C, 73·7; H, 4·1%), $\lambda_{max.}$ 242, 302 mμ (log ε 5·47, 5·0).

5-Chloroindazole.—*N*-(4-Chloro-*o*-tolyl)benzamide (2·5 g.) was nitrosated as a suspension in acetic acid (15 ml.) and acetic anhydride (15 ml.) at 5—10° for 1·5 hr. with nitrous fumes. When the mixture was poured into water and ice the nitroso-compound (2·2 g., 79%), m. p. 56° (decomp.), separated. It was dissolved in benzene (sodium-dried) and set aside for a few days. Acid-extraction of the benzene solution gave 5-chloroindazole, m. p. 142—143°, as needles. Its picrate had m. p. 190—192°. von Auwers and Schwegler [16] record m. p.s 143—144° and 194—195°, respectively.

Attempts to prepare N-(*2-Fluoro-o-tolyl*)*benzamide.*—A Balz–Schiemann reaction on 2-nitro-*m*-toluidine gave a fluorine-containing oil which on reduction in various ways (stannous chloride, or iron and ammonium chloride,[17] or catalytically with Raney nickel) gave a fluorine-free amine. This was identified as *o*-toluidine (by its benzoyl derivative).

Fluorine-substituted Acylanilines.—*o*- and *p*-Fluoronitrobenzene were reduced with iron and ammonium chloride according to Finger and Reed's method,[17] in 95% yield, and then acylated in the usual way. All m. p.s agreed with those given in the literature.[18]

Acylarylnitrosamines.—The required anilides were dissolved in acetic acid and acetic anhydride (1 : 1) and converted into nitroso-compounds with nitrous fumes as previously described.[4] *o*-Fluoroacetanilide gave a liquid nitroso-compound which was purified by washing its benzene solution with ice-water until neutral. A list of new nitroso-compounds thus made is attached.

Nitroso-compounds.

	Yield (%)	M. p. (decomp.)		Yield (%)	M. p. (decomp.)
N-p-Fluorophenylbenzamide	70	64°	*N-o*-Fluorophenylacetamide	68	Liquid
N-p-Fluorophenylacetamide	75	47	*N-m*-Fluorophenylacetamide	70	60°
N-o-Fluorophenylbenzamide	70	50			

Decomposition of Acylarylnitrosamines in Benzene.—A solution of the acylarylnitrosamine (1·5—3·0 g.) in benzene (100 ml.) was set aside for 3 days, then filtered, and the filtrate extracted with dilute sodium hydroxide solution and then washed with water and dried ($MgSO_4$). Evaporation left usually an oily residue. This was treated with 20% aqueous sodium hydroxide under reflux, and the alkaline mixture steam-distilled to remove fluorinated biphenyls.

[15] Davies, *J.*, 1955, 2412.
[16] von Auwers and Schwegler, *Ber.*, 1920, **53**, 1226.
[17] Finger and Reed, *J. Amer. Chem. Soc.*, 1944, **66**, 1972.
[18] Schiemann and Pillarsky, *Ber.*, 1929, **62**, 3041; Wallach and Heusler, *Annalen*, 1890, **235**, 267; Ingold and Vass, *J.*, 1928, 421.

Acidification of the residue gave hydroxybiphenyls. 4-Benzoyloxybiphenyl was separable (in an experiment with *N*-*p*-fluorophenyl-*N*-nitrosobenzamide) because of its insolubility in ether. Products were identified by mixed m. p. determinations with authentic samples. Results of these decompositions are tabulated.

Decomposition products of acylarylnitrosamines in benzene.

N-Nitroso-compound of	Substituted biphenyls
N-*p*-Fluorophenylacetamide (1·4 g.)	4-Fluoro- (0·24 g.), 4-hydroxy- (0·32 g.)
N-*p*-Fluorophenylbenzamide (3·3 g.)	4-Fluoro- (1·2 g.), 4-benzoyloxy- (1·2 g.)
N-*o*-Fluorophenylacetamide (1·0 g.)	2-Fluoro- (0·2 g.), 2-hydroxy- (0·24 g.)
N-*o*-Fluorophenylbenzamide (1·8 g.)	2-Fluoro- (0·4 g.), 2-hydroxy- (0·5 g.)
N-*m*-Fluorophenylbenzamide (5·0 g.)	3-Fluoro- (1·2 g.)

Decomposition of N-p-*Fluorophenyl*-N-*nitrosobenzamide in Nitrobenzene.*—A solution of the nitroso-compound (2·0 g.) in nitrobenzene (30 ml.) was set aside for 3 days, and the solvent then driven off by vacuum-distillation. The tarry residue was dispersed on calcium carbonate, dried, and extracted with light petroleum (b. p. 60—80°) (Soxhlet). This gave an oil (1·6 g.) from which 4-benzoyloxy-4′-nitrobiphenyl [19] (0·15 g.), m. p. 208°, was isolated because of its insolubility in ether. The latter compound yielded 4-hydroxy-4′-nitrobiphenyl,[20] m. p. 198—200°, and benzoic acid on hydrolysis. The ether-soluble portion deposited 4-benzoyloxy-2′-nitrobiphenyl [19] (0·15 g.) as yellow needles, m. p. 155—156°. All nitrobiphenyls were identified by mixed m. p. with authentic specimens.

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ROYAL TECHNICAL COLLEGE, SALFORD, LANCS. [*Received, January 13th,* 1960.]

[19] Jones and Chapman, *J.*, 1952, 1829.
[20] Bell and Kenyon, *J.*, 1926, 3044.